Virchows Archiv (2018) 472:311–313
https://doi.org/10.1007/s00428-018-2320-6

INVITED EDITORIAL

World Health Organization 4th edition of head and neck tumor classification: insight into the consequential modifications

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Received: 5 February 2018 / Accepted: 8 February 2018 / Published online: 15 February 2018

In this editorial, we provide a broad review of the consequential modifications in the newly released 4th edition of the WHO head and neck tumor classification, comment on two selected reviews in this volume of the journal, and succinctly discuss the changes made in the salivary gland tumor chapter [1–3]. In general, the new edition represents a streamlined and simplified version from previous editions in an effort to reduce redundancy and to maintain consistency within and between different chapters and topics [4]. This task has been achieved through presenting tumor entities to the sites of their most common occurrence and presentation. Sometimes, however, exceptions to this rule have been made in limited entities for either prominence or their relevance to diagnosis and differential diagnosis at certain sites. For the first time in this edition, chapters devoted to the oropharyngeal and the neck region were established. Their inclusion was based on the distinctive structures and tumor types and their relevance to the differential diagnosis and management of patients with tumors at these regions, especially regarding HPV-associated squamous cell carcinoma for the oropharynx which bears profound epidemiologic and therapeutic consequences. Efforts were also made to adopt similar nomenclature and classification of entities commonly included in other WHO tumor classifications of different organs. This is particularly notable in the classification of neuroendocrine tumors, paraganglioma, soft tissue, and lymphoreticular disorders.

In this volume of the journal, together with this editorial, detailed reviews of the significant changes that have been implemented in the nasal, paranasal and skull base, and odontogenic tumor chapters are thoroughly presented [2, 3]. In these reviews, the authors addressed the rationale for accepting new entities and modifying nomenclatures and classification of others. The nasal skull-base section, in particular, detailed the characteristics of newly accepted entities and addressed the status of certain emerging entities to clarify their use in diagnosis and differential diagnosis. Similarly, the review of the odontogenic chapter addresses the wide-ranging changes and modifications in comparison to previous editions of the blue book. In particular, the inclusion of odontogenic cysts represents a significant addition that was felt to be integral to the differential diagnosis of several odontogenic tumors. The review also addresses changes in terminology, neoplastic nature, and the inclusion and exclusion of certain lesions; the outcome being a significant reduction in the number of entities within the group odontogenic lesions. We fully contend that awareness of these changes is critical to the implementation of these pathologists for modification for consistent diagnosis and proper management of these tumors.

Several notable changes have also been made in the salivary gland tumor chapter. Among these is the inclusion of hyperplastic conditions with significant differential diagnostic relevance encompassing sclerosing polycystic adenosis, nodular oncocytic hyperplasia, and intercalated duct hyperplasia [5, 6]. Similar to the policy for other chapters in the 4th edition, the discussion of lymphoproliferative disorders in the salivary tumor chapter was limited to those commonly identified in salivary glands with a focus on extranodal marginal zone and mucosa-associated lymphoma (MALT syndrome) as the most common type of lymphomas, in this area [7]. Because of their commonly shared features and presentations, both exophytic and inverted ductal papillomas were combined

See related article, https://doi.org/10.1007/s00428-017-2182-3; https://doi.org/10.1007/s00428-017-2116-0

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and presented in the chapter under one single heading [8, 9]. Also, a simplified grading system for mucoepidermoid carcinoma was achieved [10]. For adenoid cystic carcinoma, the concurrent finding of different forms coexisting within any given tumor precludes reliable and consistent grading and a two-tiered simplified system based on the presence or absence of a solid component was adopted [11, 12].

Furthermore, a decision to omit the deterministic "low grade" designation was made. This particularly pertains to polymorphous adenocarcinoma where labelling this lesion as low grade would preclude patients with an occasionally observed aggressive clinical behavior from being enrolled in clinical trials of high-grade salivary carcinomas [13–15]. Additionally, considerable efforts were made to place rare subtypes of adenocarcinoma under a single pathologic entity especially those with similar clinical characteristics and behavior. Among these are adenocarcinoma subtypes including intestinal-type, cribriform, and mucinous adenocarcinomas which were placed under Adenocarcinoma, NOS [16, 17].

The only new entity accepted in this chapter is secretory carcinoma (mammary analogue secretory carcinomas) as an entity separate from acinic cell carcinoma. In the past, the lack of firm features to classify these tumors has led to empirically include them with acinic carcinoma as the most closely related phenotype [18, 19]. Nowadays, a sufficient number of publications have detailed the morphologic features, immunohistochemical markers, and the molecular identification of the ETV6-NTRK-3 fusion in multiple variable techniques, justifying its recognition as a new entity [20, 21]. Given the multilineage nature of this fusion and its association with mesenchymal, lymphoreticular, and epithelial neoplasms, its diagnostic role in this entity is unclear. The ETV6-NTRK3 fusion transcript, however, induces the activation of critical cellular pathways involved in proliferation, apoptosis, and migration which can be targeted by small molecule inhibitors in future management of advanced disease [22, 23].

Among the morphologic spectrum of polymorphous adenocarcinoma, a cribriform-papillary component with clear nuclear features is variably present. In view of this, some authors have advocated to acknowledge the existence of a predominantly cribriform subtype with distinctive aggressive behavior that should be separated from polymorphous adenocarcinoma. A consensus agreement on whether to accept this form was not reached and, therefore, this variant was provisionally put within the rubric of "emerging entities." [14] Also, an attempt to specify the type of carcinoma arising within pleomorphic adenoma has been made. To clarify the generic diagnosis of carcinoma ex. pleomorphic adenoma, requirements to specify the type and nature of the carcinoma component as well as the extent of extracapsular spread were introduced, emphasizing the need to distinguish between intracapsular, minimally invasive, and widely invasive lesions [24].

Throughout this chapter, the discussions of lineage and immune-based markers were limited to those with practical diagnostic relevance. While acknowledging the importance of molecular markers in the future assessment of salivary gland tumors, the present lack of clinical utility precludes their use in current clinical practice. Accordingly, the discussion of genetic alterations including the presence of fusion genes and their relevance was aimed to be informative in the context of their potential biological and therapeutic implications.

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